

REMARKS

Claims 1-35 are pending in the present application. Claims 15, 16, 31 and 32 have been withdrawn from consideration. Claims 1-14, 17-30 and 33-35 were considered on the merits. In the present response, claim 1 and claim 17 have been amended. The amendments to the claims provide that the loss of the proteoglycan content can be measured without the use of a radioactive agent. Support for these amendments can be found throughout the specification and claims as originally filed including at paragraphs [0044], [0045], [0053], and [0056]. The amendments to the claims do not add new matter and are otherwise proper. Applicants respectfully request the Examiner enter the amendments in their entirety.

In the final Office Action, the Examiner continued to reject all of the claims based on the 35 U.S.C. § 103 grounds as set forth previously in other Office Actions. Applicants believe that the claim amendments and the enclosed declaration demonstrate that the rejection of the claims under 35 U.S.C. § 103 is improper and should be withdrawn

I. Claim Rejections – 35 U.S.C. §103**A. Kai *et al.* in view of Masuda *et al.***

In the Office Action, claims 1-8, 10, 14, 17-24, 26, 29-30 and 33 continue to be “rejected under 35 U.S.C. 103(a) as being unpatentable over Kai *et al.* (JP 2001 089390 A) in view of Masuda *et al.* (US 6197061 B1).” Applicants continue to traverse this rejection. As stated in §2143 of the MPEP,

[t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

Applicants respectfully submit that a *prima facie* case of obviousness has not been established.

First, the combination of Kai *et al.* and Masuda *et al.* fail to teach or suggest all of the claim limitations because the references fail to teach where proteoglycan degradation can be measured without the use of a radioactive agent. As set forth in the enclosed Masuda declaration, it is only the present invention that provides for the measurement of proteoglycan degradation without radioactivity. Masuda declaration, paragraph 6. In fact, the Masuda *et al.* reference cited by the Examiner teaches that radioactivity such as ³⁵S-Sulfate is used to measure proteoglycans. Masuda *et al.*, col. 11, line 7. Therefore, because Kai *et al.* and Masuda *et al.*, even in combination, fail to teach every limitation of the presently claimed methods, a *prima facie* case of obviousness has not been established and Applicants respectfully submit that the 35 U.S.C § 103 rejection be withdrawn and the claims be allowed to issue.

Second, Applicants once again submit that contrary to the Examiner's assertion, the rapid degradation of the cartilage tissue is not an inherent property of the tissue of Masuda *et al.* In response to the Applicants' argument that the rapid degradation is not inherent, the Examiner states that because the tissue in the present invention and the tissue in Masuda *et al.* are cultured in the same manner, the trait of rapid proteoglycan turnover must be inherent to both inventions. However, the Examiner is merely taking an example of a culture method in Masuda and applying it to the present invention. Masuda *et al.* do not require that the tissue be cultured exactly as in the example. In fact, Masuda *et al.* specifically state that that "mechanical properties of the cartilage matrix can be controlled by increasing or decreasing the amount of time that the cartilage tissue is cultured on the membrane. Longer culture time will result in increased crosslink densities." Col. 8, lines 41-45. See paragraph 5 of Masuda declaration.

As the MPEP states under section 2112, "the fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic" (emphasis in original). The MPEP further states that:

In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art.

To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by

probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.

MPEP §2112 under the heading “Examiner Must Provide Rationale or Evidence Tending To Show Inherency” (emphasis in original).

In the final Office Action, the Examiner implies that Applicants are admitting that the rapid degradation of the tissue where the tissue loses roughly half of its proteoglycan content in 24 hours is inherent in the tissue of Masuda *et al.* The Examiner appears to believe that the Applicants previous statement that “Applicants have recognized a previously unappreciated trait found in select samples of engineered cartilage tissues disclosed by Masuda *et al.*” supports this contention. However, the Examiner fails to appreciate that Applicants are merely pointing out that rapid degradation of the tissue in Masuda *et al.* is only found in select (not all) samples. Applicants’ statement does not show that rapid degradation of the engineered cartilage tissue is inherent in the tissue of Masuda *et al.*, instead it demonstrates that the rapid degradation of the engineered cartilage tissue is NOT inherent. See paragraph 5 of Masuda declaration.

The engineered cartilage of Masuda *et al.* changes with time in culture. See paragraph 5 Masuda Declaration. Greater time in culture results in increased crosslink densities, making the tissue of Masuda *et al.* behave more like native cartilage tissue. Masuda *et al.*, Col. 7, line 15. In this form, the tissue of Masuda *et al.* cannot be used in the present methods as native-like forms of the tissue of Masuda will take longer than 24 hours to produce 50% proteoglycan release. Thus, it is evident that how the tissue of Masuda *et al.* is cultured directly influences the time frame for proteoglycan release. Thus, rapid degradation is simply not a property that necessarily flows from the tissue of Masuda *et al.* See paragraph 5 Masuda declaration. The Masuda *et al.* tissue is not like aspirin with a fixed composition and inherent properties. One must choose to culture the tissue in a specific way to obtain the property of rapid degradation for use in the claimed methods, and until the present invention, this particular response based on culture time was unknown. See paragraph 5 of Masuda declaration. Neither Masuda *et al.* nor Kai *et al.* teach any such selection and use of engineered cartilage.

Based on the foregoing arguments, Applicants respectfully submit that because the Kai *et al.* and Masuda *et al.* references, even when combined, fail to teach the required limitation of rapid degradation of the engineered cartilage matrix where the cartilage matrix loses roughly half its proteoglycan content within 24 hours after treatment, the references do not teach every element of the claimed invention and cannot render claim 1 and claim 17 obvious. As claims 2-8, 10, 14, 18-24, 26, 29-30 and 33 all depend either directly or indirectly from claim 1 or claim 17, the cited art fails to establish a *prima facie* case of obviousness for these claims as well. Therefore, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) based on the combination of Masuda *et al.* and Kai *et al.* be withdrawn.

B. Purchio *et al.* in view of Masuda *et al.*

The Examiner continues to reject claims 1-10, 14, 17-26, 33 and 35 “under 35 U.S.C. 103(a) as being unpatentable over Purchio *et al.* (US 5,902,741) in view of Masuda.” Once again, Applicants traverse this rejection.

Purchio *et al.* in combination with Masuda *et al.* fail to establish a *prima facie* case of obviousness. Even when taken together, Purchio *et al.* and Masuda *et al.* do not teach a method requiring rapid cartilage tissue breakdown, wherein the cartilage tissue loses roughly half its proteoglycan content within 24 hours after treatment and further wherein the proteoglycan content can be measured without the use of a radioactive agent.

Neither Purchio *et al.* nor Masuda *et al.* teach or suggest where proteoglycan content can be measured without the use of a radioactive agent. In fact, Masuda *et al.* teach the use of ³⁵S-Sulfate, a radioactive agent, to measure proteoglycan content. Nothing in Purchio *et al.* suggest that non-radioactive methods may be used. As understood by the skilled artisan, there are numerous advantages to being able to measure proteoglycan content without the use of radioactive agents. For example, when non-radioactive agents are used, there is no need for laboratory personnel to be specially trained in the use of radioactivity. Moreover, the dangers of the uses of radioactivity, such as spills and accidental exposures can be eliminated. Thus, the skilled artisan clearly understands that inventions, such as the invention provided by the present patent application, which do not require the use of radioactivity but maintain similar measurement sensitivity are extremely advantageous. As neither of the references cited by the

Examiner, either alone or in combination, teach or suggest an invention having the ability, as well as the advantages, of measuring proteoglycan content without the use of a radioactive agent, the references cannot make the present invention obvious. As this limitation is present in the independent claims, the references cited by the Examiner also fail to make the dependent claims obvious. Therefore, Applicants respectfully request the Examiner withdrawn the 35 U.S.C. § 103 rejection of claims 1-10, 14, 17-26, 33 and 35 and allow the claims to issue.

Furthermore, contrary to the Examiner's assertion, rapid degradation of the engineered cartilage tissue of Masuda *et al.* is not an inherent feature of the tissue. See paragraph 5 of the Masuda declaration and Section I.A. above. Applicants respectfully submit that because the limitation of rapid degradation of the engineered cartilage tissue, where the cartilage tissue loses roughly half of its proteoglycan content within 24 hours after treatment with Il-1 in claim 1 and claim 17 does not exist in the combination of Purchio *et al.* and Masuda *et al.*, the references do not teach every element of the claimed invention. As claims 2-10, 14, 18-26, 33 and 35 all depend either directly or indirectly from claim 1 or claim 17, the art cited by the Examiner also fails to teach and every element of these claims. Thus, Applicants respectfully request the Examiner withdraw the rejection and allow claims 1-10, 14, 17-26, 33, and 35 to issue.

C. Saito *et al.* in view of Masuda *et al.*

In the final Office Action, claims 1-8, 17-24, 29-30 and 35 were "rejected under 35 U.S.C. 103(a) as being unpatentable over Saito *et al.* in view of Masuda *et al.*" Applicants continue to traverse this rejection.

Yet again, a *prima facie* case of obviousness has not been satisfied as the combination of Saito *et al.* with Masuda *et al.* does not teach or suggest an engineered cartilage matrix that is cultured to be rapidly degraded, losing roughly half its proteoglycan content within 24 hours after treatment with Il-1, wherein the measurement of the proteoglycan content can be done without the use of a radioactive agent, a limitation required by independent claim 1 and independent claim 17.

Neither Saito *et al.* nor Masuda *et al.* provide for the measurement of proteoglycan content without the use of a radioactive agent. In fact, as set forth above, Masuda *et al.* teach the use of ³⁵S-Sulfate to measure proteoglycan content. Moreover, nothing in Saito *et al.* contradict the teaching of the use of a radioactive agent nor suggest that proteoglycan content can be measured without the use of a radioactive agent. For the reason that neither Saito *et al.* nor Masuda *et al.*, either alone or in combination, teach or suggest the use of a non-radioactive method to measure the amount of proteoglycan, the two references cannot make obvious the claims of the present invention. Therefore, Applicants respectfully request the Examiner withdraw the 35 U.S.C. § 103 rejection based on Masuda *et al.* and Saito *et al.* and allow the claims as amended to issue.

In addition, as set forth in Sections I.A. and I.B. above, the use of an engineered tissue cultured to be rapidly degraded is not inherent to the invention of Masuda *et al.* See paragraph 5 of Masuda declaration. Furthermore, because Saito *et al.* lack any discussion of a tissue or procedure demonstrating this trait, Saito *et al.* fail to cure this deficiency. As this element is not taught in either reference cited by the Examiner, the references cannot render the present claims obvious even if the references are taken together. Thus, a *prima facie* case of obviousness has not been established and the Examiner should withdraw the 35 U.S.C. § 103 rejection.

Moreover, there is no motivation to combine the Saito *et al.* and Masuda *et al.* references. Indeed, Saito *et al.* teach away from combining the references because, by definition, the cartilage explant of Saito *et al.* is a non-engineered tissue because it is obtained directly from an animal. As those of ordinary skill in the art will appreciate, it would be impossible to employ this “natural” tissue with the methods of Masuda *et al.* while still maintaining the essential natural character required by culture of an explant. For example, the engineered cartilage tissue used in the present invention is highly homogenous, in contrast to the “natural” cartilage tissue in cartilage explants such as those used in Saito *et al.* Although the use of engineered cartilage tissue may be advantageous in many circumstances, in some cases, such as when experimentation centers around the response of an individual animal to a test agent, it may be more advantageous to use explant culture. Explants are particularly useful when intervariability between animals is

irrelevant. Therefore, because whether a “natural” cartilage tissue or an engineered cartilage tissue is preferable may change depending on the particular application, the two types of tissue are not interchangeable as suggested by the Examiner.

As the combination of Saito *et al.* with Masuda *et al.* does not satisfy the *prima facie* case requirements for demonstrating obviousness of independent claim 1 and independent claim 17, and because claims 2-8, 18-24, 29-30 and 35 all depend either directly or indirectly from claim 1 or claim 17, Applicants respectfully request that the 35 U.S.C. §103(a) rejection based on these art references be withdrawn. Applicants respectfully assert that the claims are now in condition for allowance.

D. Huch *et al.* in view of Masuda *et al.*

The Examiner continues to reject claims 1-11, 17-27 and 29-30 “under 35 U.S.C. 103(a) as being unpatentable over Huch *et al.* (1997) in view of Masuda *et al.*” This rejection must also fail for the reasons discussed above, and, in particular, those reasons relating to the combination of Kai *et al.* and Masuda *et al.*

Huch *et al.* combined with Masuda *et al.* does not teach or suggest all of the claim limitations in the independent claims; namely the combination fails to teach or suggest use of an engineered cartilage matrix cultured to be rapidly degraded, losing roughly half its proteoglycan content within 24 hours after treatment, wherein the proteoglycan content can be measured without the use of a radioactive agent.

First, both Huch *et al.* and Masuda *et al.* teach the quantification of proteoglycans using ³⁵S-Sulfate, a radioactive marker. As set forth in Huch *et al.*, “incorporation of ³⁵S-Sulfate into proteoglycans was quantified during the last 4 hours of culture and reported as counts per minute per µg DNA.” Huch *et al.* page 2157, col. 1. Neither Huch *et al.* nor Masuda *et al.* teach or suggest either the disadvantages of using a radioactive marker or that non-radioactive methods will be sensitive enough to measure proteoglycan content. As Huch *et al.* and Masuda *et al.*, even in combination, fail to disclose every element of the independent claims of the present invention, the references cannot render the currently pending claims obvious. Therefore, Applicants respectfully submit that the 35 U.S.C. § 103 rejection is improper and should be withdrawn.

Second, neither reference teaches a cartilage tissue with rapid degradation. In fact, degradation of chondrocyte cells similar to the cells in Huch *et al.* occurs at a much slower pace than degradation of the engineered tissue of the present invention. Aydelotte *et al.*, Articular Cartilage and Osteoarthritis 237, FIG. 2 (1992) (previously submitted). Thus, using the cartilage of Huch *et al.* with the methods of Masuda *et al.*, in the manner suggested by the Examiner, results in an assay with a different and slower speed of cartilage degradation beyond the scope of the present claims. The rapid tissue degradation of the present claims lends itself to high throughput screening, which is advantageous for many reasons. Additionally, as set forth above in Section I.A., the rapid degradation is not an inherent quality of the tissue of Masuda *et al.*

Because even when combined, Huch *et al.* and Masuda *et al.* fail to teach all the limitations of the present invention, the combination of Huch *et al.* and Masuda *et al.* fails to establish a proper *prima facie* case of obviousness. Thus, Applicants respectfully request the Examiner withdraw this rejection and allow independent claim 1 and independent claim 17, as well as claims 2-11, 18-27 and 29-30 which depend therefrom, to issue.

E. Lansbury *et al.* in view of Masuda *et al.*

Finally, in the final Office Action claims 1-8, 10, 14, 17-24, 26 and 33 were once again “rejected under 35 U.S.C. 103(a) as being unpatentable over Lansbury *et al.* (WO 94/28889) in view of Masuda *et al.*” This combination also does not state a *prima facie* case of obviousness for the reasons discussed above, *e.g.*, the combination does not teach or suggest all of the elements of the claimed invention, such as the use of engineered cartilage tissue cultured to be rapidly degraded, losing roughly half its proteoglycan content within 24 hours after treatment with Il-1, wherein the proteoglycan content can be measured without the use of radioactivity.

In contrast to providing methods wherein proteoglycan content can be measured without the use of radioactivity, both Lansbury *et al.* and Masuda *et al.* describe the measurement of proteoglycans using ³⁵S-Sulfate. Lansbury *et al.*, page 24, line 16. Lansbury *et al.* even go as far as to include another radioactive method that can be used to measure proteoglycan content. Lansbury *et al.*, page 25, line 35. Because both Lansbury *et al.* and Masuda *et al.* teach away from the use of non-radioactive methods to measure proteoglycan content, Lansbury *et al.* and Masuda

et al. fail to teach every limitation of the presently pending claims. Thus, the Examiner has failed to establish a *prima facie* case of obviousness.

In light of the lack of establishment of a *prima facie* case of obviousness, Applicants respectfully request the Examiner withdraw this rejection and allow the claims to issue.

CONCLUSION

In view of the above remarks, it is respectfully submitted that this application is in condition for allowance. Early notice to that effect is earnestly solicited. Examiner Davis is invited to contact the undersigned at the number listed below if she believes such would be helpful in advancing the application to issue.

Respectfully submitted,

Date March 23, 2005

By Kathryn E. Cox

FOLEY & LARDNER LLP
Customer Number: 23524
Telephone: (608) 258-4277
Facsimile: (608) 258-4258

Kathryn E. Cox
Attorney for Applicants
Registration No. 55,089